

# Stress, coping and resilience in an ageing population

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## Chapter 7: Stress, coping and resilience in an ageing population.

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### *Introduction*

Ageing is a physiological process that is part of normal development (Cutler, 1991). However, the **stress response** in humans, although an adaptive mechanism initially, has the potential to be chronic and detrimental to the organism if too large and/or prolonged (Sapolsky, 2007). This particularly appears to be the case later in the lifespan; in fact some of the changes in older age mirror the chronic effects of stress on several of the body's biological systems. This chapter will mainly focus on the impact of stress on the **immune system** and the implications for resilience in older age, as stress effects on all bodily systems are beyond the scope of one chapter. Further, the immune system undergoes several changes with ageing, resulting in increased susceptibility to infectious and autoimmune diseases and cancer, all of which are also influenced by stress.

### *The stress response*

The physiological response to stress was characterized by Walter Cannon (1929) as the 'fight or flight' response. The main function of this response is to maintain bodily homeostasis. Biologically, the key site involved in this process is the hypothalamus (Barrett, 2005), a part of the brain that communicates by sending nerve impulses to other parts of the body. In this way, the hypothalamus acts within seconds and via the sympathetic nervous system stimulates the medulla of the adrenal gland to release catecholamines (adrenalin and noradrenalin) which act on receptors throughout the body to result in several effects such as increased heart rate, blood pressure and

respiration, activation of smooth muscle, and increased core temperature and pain threshold (Charmandari, Tsigos, & Chrousos, 2005). In addition, the hypothalamus also produces chemical messengers that act more slowly and in the next minutes travel through the **hypothalamic-pituitary-adrenal (HPA) axis** (Sapolsky, Romero, & Munck, 2000). Chemical messengers in this pathway include corticotrophin releasing hormone (CRH) which stimulates anterior pituitary gland to release another hormone, adrenocorticotrophic hormone (ACTH), into circulation. The target organ of ACTH is again the adrenal gland, but this time it is the cortical cells that synthesise and release species-specific glucocorticoids (GC) into the blood. The tight control of these GC (mainly cortisol in humans) is sustained via negative feedback that controls and terminates the release of CRH (Griffin & Ojeda, 2004). **Cortisol** potentiates the effects of catecholamines within the body (Charmandari, et al., 2005) as well as initially activating the immune system, then later working as an anti-inflammatory agent generally suppressing immune function, to prevent harmful over-activation (Munck, Guyre, & Holbrook, 1984). However, when stress is prolonged, chronic, or there are repeated exposures to stressful events, dysregulation of the stress response axis can occur resulting in detrimental effects throughout the body, for example, on the cardiovascular system (McEwen, 1998; Phillips, 2011; Sedova et al., 2004) and also by suppression of the immune system (Sorrells & Sapolsky, 2007).

### *The immune system*

The immune system can be considered as two distinct, but interconnected elements; the innate and the adaptive immune systems. The innate response is often referred to as the 'first line of defence' against infection as it comprises mechanisms that are the first to react to an infection. The adaptive immune system is slower to respond but has the advantage that it includes memory of pathogens encountered and that its response is specific for each pathogen, thus conferring a tailored and long lasting protection against further infection by the same pathogen. The innate immune system consists of soluble components, namely the complement system, and cellular elements, including neutrophils which deal with rapidly dividing bacteria and fungi, eosinophils which respond to parasitic infections, macrophages which secrete soluble factors (such as the

cytokines  $\text{TNF}\alpha$ , IL-1, IL-6) to co-ordinate and amplify the immune response and also provide immunity against intracellular bacteria, and Natural Killer (NK) cells which detect and kill virally-infected and tumour cells. Adaptive immunity is provided by T and B lymphocytes, which develop and mature in the thymus and bone marrow respectively. T cells can be further classified into CD4 expressing helper cells (which in turn can be split into Th1 and Th2 types), CD8 expressing cytotoxic cells and CD25 expressing T regulatory cells, which have immune suppressive function. B cells, when presented with antigen (by dendritic cells or with T cell help) produce **antibody** to provide extended protection against infections. When a naïve T or B cell encounters a pathogen it will proliferate and differentiate into an effector cell or a memory cell, so that if the pathogen is encountered a second time a more rapid response can be achieved. Ageing is known to have deleterious effects upon both the innate and adaptive immune responses, though the latter is much better characterized (A.C. Phillips, V.E. Burns, & J.M. Lord, 2007).

### *Ageing and immunity*

With ageing, innate immune response goes through some changes. For example, complement activation appears to be unaffected, but neutrophil bactericidal and phagocytic function *in vitro* is dramatically reduced (Butcher et al., 2001). Macrophage function is also modified, although the literature is rather contradictory, including reports of reduced phagocytosis and superoxide function as seen in neutrophils, but enhanced secretion of the cytokines IL-6 and IL-8 in response to mitogen and lipopolysaccharide (LPS). NK cells are also affected by ageing; while their numbers do not change with age, their cytotoxic capacity is reduced (Hazeldine, Hampson, & Lord, 2012) which has also been shown to relate to reduced survival in people aged over 75 years (Ogata et al., 2001). In the adaptive immune system, the thymus gland atrophies and thus fewer naïve T cells are produced. As the size of the T cell pool is maintained at a constant level, the proportion of T cells that are memory cells increases. Consequently, as we age, we are less able to deal with new pathogens. In addition to changes in the ratio of naïve to memory T cells, there is a shift from T-helper 1 to T-helper 2 cells, and the end

result is reduced cell-mediated, Th1-type, immunity. Finally, with ageing, antibody production in response to antigen declines; for example, older people produce a lower antibody titre in response to **vaccination** than younger individuals and the antibodies produced are of lower affinity. This is thought to be largely the result of a decline in T cell help for B cells in older adults.

Another concept that frequently appears in the literature when discussing the ageing of the immune system is **inflammageing** (Franceschi, Capri, Monti, Giunta, Olivieri, Sevini, Panourgia, et al., 2007). Inflammageing indicates an imbalance between inflammatory factors necessary to fight the infection, but is damaging in excessive amounts, and anti-inflammatory components act as a counter weight. It has been suggested that ageing and longevity could, therefore, potentially be dependent on this balance (Franceschi, Capri, Monti, Giunta, Olivieri, Sevini, Panouraia, et al., 2007). This would mean that immunosenescence, together with inflammatory markers such as different cytokines (IL-6, IL-8 and IL-15) could contribute to the prediction predictors of the longevity of organisms.

### *Stress hormones and ageing*

As outlined above, stress, whether physical or psychological, is broadly sensed by two systems within the hypothalamus, the HPA axis and the sympathetic-adrenal-medullary system. Stress induces the release of catecholamines from the adrenal medulla, and both cortisol and **dehydroepiandrosterone** (DHEA) from the adrenal cortex. Catecholamines and cortisol can both be immunosuppressive if chronically elevated. In contrast, DHEA is a precursor to sex hormones and is considered to be immune enhancing (Butcher et al., 2005). Due to the impact of these hormones on immunity, any change in their production could therefore have significant health implications. In humans, the production of DHEA and its sulphated form, DHEAS, declines with age, a process termed the adrenopause (Orentreich, Brind, Rizer, & Vogelmann, 1984). The synthesis of DHEA is maximal in humans at age 20-30 and declines gradually

thereafter, so that by the seventh decade levels of DHEA can be as low as 10% of that seen in young adulthood (Orentreich, Brind, Vogelman, Andres, & Baldwin, 1992). This **adrenopause** occurs at similar rates in both males and females and is a physiological phenomenon unique to the higher primates. However, although DHEA/S levels fall with age the production of glucocorticoids such as cortisol is remarkably unaltered (Orentreich, et al., 1992), resulting in a relative excess of cortisol over DHEA/S and an imbalance of immune suppression over immune enhancement. The age-related immunological and endocrinological changes outlined above may have implications for resilience to stress in older adults. It is likely that the combination of adrenopause, leading to a relative preponderance of cortisol, and an already reduced immune defence against infection through immune senescence, may leave this population particularly vulnerable to the negative effects of stress on immunity (Graham, Christian, & Kiecolt-Glaser, 2006; A. C. Phillips, V.E. Burns, & J. M. Lord, 2007).

### ***Caregiver stress and immunity in ageing***

One commonly studied model of the impact of stress on immunity is role of caring for someone, be it a spouse or child with a physical or mental illness or disability. Older caregivers have most commonly been studied in this context, using the model of family dementia caregiving (Gouin, Hantsoo, & Kiecolt-Glaser, 2008). Caregiving is now well established as having a serious effect on psychological well being, physical health and self-efficacy among caregivers when compared to matched non-caregiving individuals (Pinquart & Sorensen, 2003). Both innate and adaptive immunity are affected by chronic stress experienced by older adults. For example, wound healing was slower in older dementia caregivers when compared to age, sex and income-matched controls (J. K. Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995). Wound healing is a complex process comprised of various phases (immediate response, inflammatory response, proliferation, migration and contraction and resolution) that activates many different cells and molecules (Shaw & Martin, 2009). Cells such as neutrophils and macrophages, and high concentrations of cytokines are main players in inflammatory phase with a role to protect from invading pathogens and set the conditions for the repair process (Shaw & Martin, 2009). Lower production of proinflammatory cytokines

involved in the wound healing process such as IL-1 $\alpha$ , IL-8 (Glaser et al., 1999), as well as IL-1 $\beta$  (J. K. Kiecolt-Glaser, et al., 1995) seen in caregivers compared to the controls, indicates the possibility of a direct effect of stress on cytokine production in wound healing. NK cells' ability to kill target tumour cells between older dementia caregivers and controls was not different (M. Irwin et al., 1991), but in the presence of cytokine stimulation this similarity between stressed individuals and controls was not preserved; NK cells from caregivers responded more weakly compared to those from the controls (Esterling, Kiecolt-Glaser, Bodnar, & Glaser, 1994). All this, together with the stress-induced reduction in IFN- $\gamma$  production (Glaser, Rice, Stout, Speicher, & Kiecolt-Glaser, 1986), indicates cytokines as a common target of the impact of chronic stress exposure, and a potential effector through which much immune suppression may occur.

A further association with the chronic stress of caregiving was found for adaptive cell mediated immunity; elevated cortisol levels as well as poorer proliferation to antigen and lower IL-2 production was shown in the caregiving group (M. E. Bauer et al., 2000). Caregiving stress in older adults has also been shown to be associated with the T-helper 1 to T-helper 2 shift in the type of cytokine responses, with the difference that in the older stressed individuals this was driven purely by an increase in IL-10 production, with no difference in IFN- $\gamma$  production by Th1 cells (Glaser et al., 2001). It is likely that stress-induced changes in catecholamine levels (Elenkov & Chrousos, 2002) during the psychological stress response drive this cytokine-related behaviour.

Inflammageing, as observed in the elderly, might also be more severe among chronically stressed older adults, such as dementia caregivers. Indeed, when compared to non-caregiving older adults who also had immunosenescence, not only did older caregivers show higher levels of IL-6 (von Kanel et al., 2006), but its rate of increase was four times higher than in non-caregiving elderly controls, leaving them particularly vulnerable to IL-6 related diseases such as frailty, cardiovascular diseases, osteoporosis and others (Ershler & Keller, 2000).

In terms of humoral immunity, caregivers but only those aged over 60 years showed lower levels of a particular antibody, salivary immunoglobulin A, which targets pathogens in biological fluids, particularly saliva at mucosal surfaces (Gallagher et al., 2008). A novel approach for assessing the severity by which caregiving stress affects the immune system of older caregivers is that of studies of latent-virus antibody titres. It is known, for example, that reactivation of latent viral infections, such as those initiated by Herpes group (HSV-1, EBV, and CMV) is typical for immunosuppressed patients such as HIV and transplant patients (Rasmussen, 1991). Interestingly, older spousal caregivers had higher IgG antibody titers against EBV VCA (virus capsid antigen) compared to the matched controls, indicating poorer control of the latent infection in this group (J. K. Kiecolt-Glaser, Speicher, Glaser, Dura, & Trask, 1991). Together with the higher antibody titre to total viral antigen of HSV-1, caregivers also had a decreased virus-specific T cell response; another component of immune system necessary for controlling the infection (Glaser & Kiecolt-Glaser, 1997). Older caregivers have also been characterised by higher antibody titres against CMV when compared to the controls (Pariante et al., 1997).

**Vaccination** responses are affected among older adults which makes them particularly vulnerable to frequent infections such as pneumonia and influenza, among the top five causes of high morbidity and mortality in this age group (Thompson et al., 2003). It would be expected that this aspect of immune incompetence would be further exacerbated in older adults affected by the chronic stress of caregiving. This is indeed the case; a significantly lower percentage of older caregivers of dementia patients showed a four-fold increase in antibody titre in response to vaccination against the influenza virus, a response that is clinically considered to be protective against infection (Vedhara et al., 1999a). This was accompanied by higher salivary cortisol concentration in the caregiver group when compared to the controls, pointing again to the role of HPA axis in immune regulation among chronically stressed individuals. Most antigens, however, trigger both humoral, i.e., the antibody response which is generated by B lymphocytes, as well as cellular responses, mainly mediated by cytotoxic CD8+ T-cells (R. Glaser, J. Sheridan, W. B. Malarkey, R. C. MacCallum, & J. K. Kiecolt-Glaser,



2000a; J. K. Kiecolt-Glaser, R. Glaser, S. Gravenstein, W. B. Malarkey, & J. Sheridan, 1996; Siergist, 2008). In addition, CD4+ helper T-cells are necessary as mediators between those two. It has been shown that both the antibody response to medical vaccination against the influenza virus, as well as IL-2 production in response to antigen stimulation, was lower in caregivers comparing to the controls (Kiecolt-Glaser et al., 1996). In the case of the pneumococcal pneumonia vaccine, even though caregivers managed to exert an adequate immune response initially, shown as a rise in IgG antibody titre, it declined over time more rapidly in this group than in the group of matched controls, likely either as a consequence of decrease in number of antibody-specific B-cells, or their ability to produce antibody (Glaser, et al., 2000a; Vedhara, et al., 1999a).

Finally, even the effect of molecular mechanisms in ageing appears to be exacerbated by chronic stress in older adults. Telomere shortening is commonly used as an index of biological ageing (Wolkowitz et al., 2011), which contributes to increased incidence of age-related diseases (M.E. Bauer, 2005; Blasco, 2005). Telomeres are specialized nucleoprotein complexes at the end of chromosomes. They function to cap the chromosome, enabling recognition of the end of chromosomes as a break in DNA, thus preventing chromosomal fusions. Telomeres typically shorten during somatic cell division as a consequence of the 'end replication problem' (Olovnikov, 1973; Watson, 1972), as well as through various processes of genetic damage, with oxidative stress a potentially prominent driver of this telomere erosion. Thus, telomere length has been regarded as a biomarker of biological ageing that may help explain environmentally induced differences in rates of ageing, such as those associated with caregiving stress (Damjanovic et al., 2007a; Epel et al., 2004) and childhood adversity (Kananen et al., 2010; Tyrka et al., 2010). Indeed, caregivers of dementia patients had shorter immune cell telomere lengths, and this was not due to having a higher number of these cells with shorter telomeres (Damjanovic et al., 2007b). On the other hand, caregivers also showed an increase in basal telomerase activity, the enzyme that works to preserve telomere length, which could indicate an attempt of these cells to compensate for the loss of their telomere length (Damjanovic, et al., 2007b).

### *Chronic stress and immunity in ageing*

Interestingly, most studies of stress and immunity in older adults have focused on the caregiver-control model outlined above, with less attention being given to elderly individuals experiencing a range of more mundane stress exposures. Although one study has reported that perceived stress, measured using the perceived stress questionnaire (Cohen, Kamarck, & Mermelstein, 1983), was associated with a poorer antibody response to the influenza vaccine in the elderly (Kohut, Cooper, Nickolaus, Russell, & Cunnick, 2002), another small scale study found no association between perceived stress and antibody status following this vaccination in elderly nursing home residents (Moynihan et al., 2004). Very few studies have focused on stressful life events, despite these being a common means of assessing the impact of stress on immunity in younger samples (e.g., (Burns, Carroll, Drayson, Whitham, & Ring, 2003; Phillips, Burns, Carroll, Ring, & Drayson, 2005)). However, a study published in 2006 examined overall stressful life events using a life events rating scale and showed that middle-aged and older adults with higher ratings of stress and disruptiveness for the stressful events they had experienced in the past two years showed lower levels of IgA in saliva (Phillips, Carroll, Evans, et al., 2006). A further study in 184 community dwelling older adults, examined the associations between stress and the antibody response to the annual influenza vaccination (Phillips, Carroll, Burns, et al., 2006). In this study, it became apparent that participants' overall stressful life events exposure was not significantly associated with the antibody response to influenza vaccination (Phillips, Carroll, Burns, et al., 2006). However, one particular life event, bereavement, was negatively associated with one-month antibody levels against two out of three of the 'flu strains contained in the vaccine. Further, these associations remained statistically significant following adjustment for age and the presence of chronic illness at baseline. The negative association between bereavement and antibody status following vaccination is in line with previous studies of bereavement and immune function. Bereavement has been associated with in vitro functional immune measures such as decreased natural killer cell cytotoxicity and poorer lymphocyte proliferation to

antigen (Bartrop, Luckhurst, Lazarus, Kiloh, & Penny, 1977; Goodkin et al., 1996; M. Irwin, Daniels, Smith, Bloom, & Weiner, 1987; Kemeny et al., 1995; Schleifer, Keller, Camerino, Thornton, & Stein, 1983; Zisook et al., 1994). In follow-up work, focussing on the two-month period post-bereavement, it was shown that neutrophils' killing ability was suppressed in bereaved older adults, an effect that was accompanied by the increase in cortisol:DHEAS ratio (R. Khanfer, J. M. Lord, & A. C. Phillips, 2011).

The absence of an association between overall life events and antibody response to influenza vaccination in the older adults and vaccination study (Phillips, Carroll, Bums, et al., 2006) contrasts with the results of previous research on young participants (Burns, et al., 2003; Phillips, et al., 2005). However, in these student studies, the modal number of life events experienced in the past year was six, with no participants reporting one or less events (Phillips, et al., 2005), whereas in the elderly sample, the modal number of major life events in the year prior to vaccination was zero, with 31% of the sample reporting no events, and a further 17% reporting only one. This might be due to differences between student and older adult life event stress scales. In the student studies, less serious events were included in the stress scale, for example, getting an unjustified low mark on a test or minor financial problems, along with more major events, whereas in older adults life events scale tend to focus on exposure to major life events. Accordingly, the absence of an association between antibody response and overall life events in older adults may reflect the use of a scale including only serious life events. However, the results for bereavement would argue against this explanation. In addition, it is also possible that the elderly simply experience fewer general life events than younger samples. There is certainly evidence to this effect: elderly individuals encountered fewer major life events than middle-aged participants in a large cohort study in the west of Scotland using the same life events measure as the present study, but retrospectively over two years. Middle-aged participants identified a mean of 2.0 events whereas the mean number of events for the elderly was 1.7 (Carroll, Phillips, Ring, Der, & Hunt, 2005). These data also suggest that our participants were not unusual in experiencing few life events, given that the mean number of events reported over one year was 2.9. Accordingly, it may be that individual differences in

general life events exposure are less important for immunity as people age, whereas bereavement, a specific life event that the elderly are more likely to encounter than the young, assumes greater prominence.

### ***Social support and immunity in ageing***

Given the substantial impact of various types of chronic stress on immunity in older adults, as outlined above, understanding psychological factors that can help to enhance or improve immunity in this group is particularly important.

Social support, or comfort, caring, esteem, or help provided by other people or social groups can be a key resource that helps individuals cope with life. It has also been shown to have a substantial impact on health, for example, individuals with low numbers of supportive relationships had two to three times the mortality risk compared to those with large social networks (Berkman & Syme, 1979). Indeed, social network size and quality and frequency of social support have been shown to impact on morbidity and mortality from serious diseases in many epidemiological studies, e.g., (Barger, 2013; House, Robbins, & Metzner, 1982; Kaplan et al., 1988). Social support has also been shown to relate to immune function. For example, whereas students who had seroconverted after the first injection of the standard three-dose hepatitis B vaccination were less anxious and reported lower stress levels, those who reported greater social support demonstrated a stronger combined immune response to the booster third inoculation (Glaser et al., 1992). In another study of college freshmen, loneliness and smaller social network size were associated with a poorer antibody response to the A/New Caledonian strain of the influenza vaccination (S. Pressman et al., in press; S. D. Pressman et al., 2005). Finally, higher social support scores, particularly higher frequency of tangible support was related to an increased antibody response to the A/Panama component of the influenza vaccination, again in university students (Phillips, et al., 2005).

In a study of social support in the elderly, social support was negatively correlated with A/Panama influenza strain antibody status following vaccination, finding which even the authors found difficult to explain (Moynihan, et al., 2004). In contrast, a larger study of

older adults considered the actual vaccination response, i.e., the change in antibody levels from pre- to post-vaccination (Phillips, Carroll, Bums, et al., 2006). In this study, although social network size and functional social support were not related to antibody response, married/cohabiting participants showed a better antibody response to the A/Panama strain at one month than those who were not married, particularly widowed, participants. Also, for those who were married or cohabiting, higher marital satisfaction was related to higher titers to A/Panama at one month. This is not entirely surprising given that poorer marital quality, in terms of adjustment and negative marital interactions, are associated with inferior functional immunity evidenced through reduced proliferation to some antigens, poorer latent virus control (J.K. Kiecolt-Glaser et al., 1987; J. K. Kiecolt-Glaser et al., 1997; J. K. Kiecolt-Glaser et al., 1988; J. K. Kiecolt-Glaser et al., 1993), and weaker natural killer cell cytotoxicity (Miller, Dopp, Myers, Stevens, & Fahey, 1999) in the general population. Further, it is possible that the variations between older care-givers and controls in terms of vaccination response (Glaser, Kiecolt-Glaser, Malarkey, & Sheridan, 1998; R. Glaser, J. F. Sheridan, W. Malarkey, R. C. MacCallum, & J. K. Kiecolt-Glaser, 2000b; J.K. Kiecolt-Glaser, R. Glaser, S. Gravenstein, W.B. Malarkey, & J. Sheridan, 1996; Vedhara et al., 1999b) may be driven, at least in part, by the effects of care-giving on marital quality and satisfaction, although more specific measurement of stressful life events and marital parameters would be necessary to support this speculation. Whatever the case, these findings resonate with the broad consensus that both marriage (Gordon & Rosenthal, 1995; House, Landis, & Umberson, 1988; Johnson, Backlund, Sorlie, & Loveless, 2000; Verbrugge, 1979), and marital satisfaction (Coyne & DeLongis, 1986; J. K. Kiecolt-Glaser & Newton, 2001; Robles & Kiecolt-Glaser, 2003) are beneficial for health. Further, it is possible that in an elderly population, general social support is less critical, whereas the specific social support resource of a happy marriage becomes more important for health, including susceptibility to infection.

Interestingly, the studies of social support and immunity show direct associations rather than an effect of social support via buffering the negative impact of stress. It is possible that for psychological and other health outcomes, social support can buffer stress

effects (Lazarus & Folkman, 1984; Rosengren, Orth-Gomer, Wedel, & Wilhelmsen, 1993), whereas for immune function, social support might impact immunity independently.

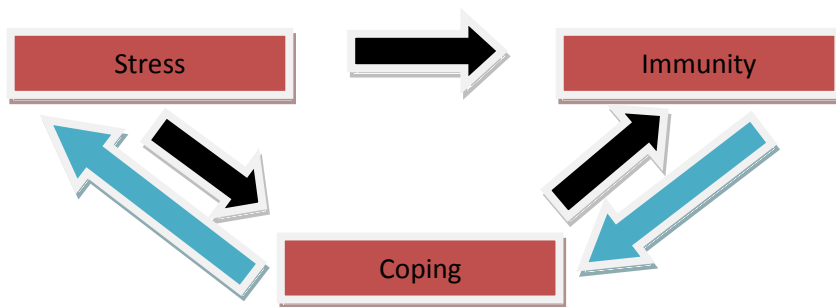
### ***Coping and immunity in ageing***

Coping, as a resource to moderate psychological stress and improve health has received little attention in the immune literature. A few exceptions include a study of law students where active coping strategies, indexed through perseverance, was associated with larger delayed type hypersensitivity responses, an index of good immune function, but only among men (Flynn, Schipper, Roach, & Segerstrom, 2009). In contrast, in students, seeking less social support related to greater lymphocyte proliferation to antigen, and lower positive reappraisal strategies related to greater IL-2 production in a non-examination period but not in the stressful pre-examination period (Koh, Choe, Song, & Lee, 2006). Interestingly, in the case of acute short-term stress, where effects on immune function are generally positive and enhancing (Dhabhar, 2000, 2002), an active coping acute laboratory stress task (memory test) can increase the concentrations of salivary antibody, while a passive coping task (surgical video) results in decreases in salivary antibody, i.e., worsened immunity (Bosch et al., 2001).

Coping and immunity research is even scarcer among older adults. One study showed that caregiving for a spouse with dementia was not related to impaired mucosal immunity measured in saliva, neither was coping (Bristow, Cook, Erzinclioglu, & Hodges, 2008). In contrast, higher levels of active coping measured by questionnaire in healthy older adults related to greater lymphocyte proliferation to antigen if participants reported high stress levels, but not if they reported low stress. In contrast, avoidance coping was associated with greater proliferation in participants with low perceived stress levels, but not at among those with high stress levels (Stowell, Kiecolt-Glaser, & Glaser, 2001). This suggests that coping interacts with individuals' perceived stress in terms of its impact on immunity, playing its main role in the presence of high stress levels. This view resonates with that described by a Dutch clinical psychologist (Olf, 1999) such that chronic stress or repeated stress exposure might outweigh and

individual's coping resources, and result in feelings of depression. Depression can lead to immune system down-regulation itself (Castle, Wilkins, Heck, Tanzy, & Fahey, 1995; Cruess et al., 2003; Glaser & Kiecolt-Glaser, 1987; M. R. Irwin & Miller, 2007; J. K. Kiecolt-Glaser & Glaser, 2002; McGuire, Kiecolt-Glaser, & Glaser, 2002; Zisook, et al., 1994). Consequently, stress itself can not only influence immunity directly via the effects of stress hormones, but also indirectly through its influence on individuals' wellbeing and their capacity to cope effectively. Further, just as stress can contribute to both depression and worsened immunity, stress effects on immune function itself can also contribute to symptoms of depression through increased inflammatory cytokine levels which induce feelings of depression (Anisman & Merali, 2003; Connor & Leonard, 1998; Cyranowski et al., 2007; Duggal, Upton, Phillips, & Lord, 2013; Trzonkowski et al., 2004). Thus, the relationship between stress, immunity and coping is multi-directional as shown in the simplified diagramme below.

**Figure 1: Stress, coping and immunity**



### *Stress resilience in ageing*

In this system pictured above, the word coping might equally be replaced by depression, as an index of coping ability exceeded. Further, stress need not be only psychological stress, but could also be physiological stress such as physical disease or physical trauma such as a severe fracture or burn. This brings us to the topic of stress resilience in later life. In ageing adults, this picture is worsened by the presence of concomitant immune senescence and adrenopause, meaning that resilience to stress and its effects is likely to be lower than in younger adults (A.C. Phillips, et al., 2007).

Indeed, older adults undergoing the stress of bereavement had both a greater cortisol:DHEA ratio and poorer immune function than non-bereaved controls (R. Khanfer, J.M. Lord, & A.C. Phillips, 2011). Similarly, older adults who experienced the physical trauma or stress of hip fracture had higher cortisol:DHEA ratios than healthy controls and lower neutrophil function (Butcher, et al., 2005), and individuals with lower neutrophil function were more likely to succumb to infection post-fracture (Butcher, Killampalli, Chahal, Kaya Alpar, & Lord, 2003). Further, older adults who developed depression post-hip fracture showed the highest cortisol:DHEA ratio and poorest neutrophil function (Duggal, et al., 2013), as well as worse frailty and slower physical recovery (Phillips, Upton, Duggal, Carroll, & Lord, 2013).

### **Conclusion**

Throughout this chapter we have attempted to describe the impact of ageing on stress hormones and immune function as well as the effects of stress on immunity and the role of stress hormones. We then summarized the research on the interacting impact of stress and ageing on immunity and health, as well as the effects of resources to reduce stress and improve immunity such as social support and coping. This brings us to the conclusion that the combination of the normal processes of ageing (adrenopause, inflammaging, immune senescence) can contribute to a reduced state of resilience to stress in later life. Consequently, those older adults with a genetic predisposition to milder adrenopause and immunosenescence, are likely to be more resilient. However,



as stress can impact on stress hormone levels and immunity even in young healthy adults, it is likely that chronic stress throughout the life span and/or reduced resources to handle the impact of stress will further impact on resilience in older adults. In this way, individuals with a life history of fewer severe stress exposures may be at lower risk of a heightened cortisol:DHEA ratio, immune decrements, and greater inflammation, even in the presence of the normal hormonal and immune changes associated with ageing. These individuals are thus likely to be more resilient to stress or trauma if and when it does occur later in the lifespan, although longitudinal research would be needed to confirm these effects of lifetime stress exposure, and the limit of where these contribute to poorer immunity is likely to differ across individuals.

Although avoiding stressful events themselves may not be a realistic undertaking for most individuals, certainly where stress levels can be reduced by changing behaviour, coping strategies or seeking social support, these methods are likely to have positive psychological, immune and thus health impact throughout life not just in older age. Healthy behaviours with direct effects on both perceived stress levels and immune function can also be pursued in order to increase resilience in later life. These would include exercise or physical activity, adequate sleep, a balanced diet, not smoking, and moderation of alcohol intake, but their effects on immunity and within healthy ageing warrant a separate chapter each.

A certain level of stress can be beneficial for health, and indeed the immune system, as has been mentioned above in the case of acute stress, by acting as a resilience enhancer much the same way a vaccine challenges the immune system but builds resilience against disease (Lewitus & Schwartz, 2009), the key to resilience in later life is getting the balance right.

- **Practical Research Tips**

- Take a lifespan approach by considering the differences between younger and older adults in terms of types of stress and social resources, so make sure you use age-appropriate psychological measures.
- In studies where you are interested in change over time, e.g., the antibody response to vaccination, always take a baseline measure of immune function first pre-vaccination, then compare this to after the vaccination.
- Remember to measure potential confounding variables such as health behaviours (sleep, alcohol intake, exercise, diet, smoking) when examining associations between stress and health, as changes in these due to stress can influence immunity and health.

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